REQUEST FOR RECONSIDERATION

Priority Determination:

For the reasons discussed below, Applicants respectfully disagree with the Examiner that the earliest date the subject matter of claims 27-29 and 32-34 finds support is 12/1/99, in PCT/US99/28301, filed 12/1/99.

Applicants submit that new claims 35-47 are supported by PCT/US99/28301. Specifically, new claims 35-47 find support at pages 10, 18, and 39. Applicants also submit that in addition to support found in PCT/US99/28301, support for the claims may be found in PCT/US98/25108, filed 12/1/98. Although the Examiner notes that PCT/US98/25108 does not identify PRO243 as human chordin, nor according to the Examiner does it enable the use of PRO243 for induction of fetal hemoglobin synthesis, Applicants submit that PCT/US98/25108 does disclose several specific, substantial, and credible utilities for the claimed invention. For example, chordin is disclosed in various therapeutic and diagnostic applications at pages 2-3, 23, 29, and 46, Figures 6A-6B and 7, and Examples 4, 5, and 30. Further, at page 20, Applicants describe the activity of PRO243 being the ability to bind and affect (block or otherwise modulate) an activity of chordin involving the regulation of notochord and muscle formation. Also for example, at pages 37, 47-51, and 73-74, PCT/US98/25108 discusses the use of the claimed invention in assays to identify binding proteins, agonists, and inhibitors of binding interactions.

Applicants further submit that in addition to support found in PCT/US99/28301, and PCT/US98/25108, support for the claims may be found in U.S. Provisional Application Serial No. 60/067411 filed on 12/3/97. For example, at pages 9-14, U.S. Provisional Application Serial No. 60/067411 discusses the preparation of chordin polypeptides. At pages 14-17, 21-23, and 28, U.S. Provisional Application Serial No. 60/067411 discusses the use of the chordin polypeptides in hybridization probes, chromosome and gene mapping, and generation of anti-sense sequences. The structure of PRO243 is set forth at page 17. Expression patterns of PRO243 are described at page 27. Expression of

PRO243 in *E.coli,* mammalian cells, yeast and baculovirus-infected insect cells is described at pages 28-31.

For at least these reasons, Applicants respectfully submit that the proper priority date for the claimed invention is at least 12/3/97. The Applicants request that the Examiner reconsider the determination of the benefit of the earlier filing date.

Formal Matters:

Applicants have submitted herewith this response a new declaration, executed by Dan Eaton, in compliance with 37 CFR 1.67(a) and respectfully request the Examiner's objection be withdrawn.

Applicants have amended the title so that it is clearly indicative of the invention to which the claims are directed and respectfully request that the Examiner's objection be withdrawn.

Submitted herewith this response is an updated BLAST result. Applicants submit that the new BLAST result satisfies the Examiners concerns and respectfully request this objection be withdrawn.

Rejection under 35 USC § 112, second paragraph:

The Examiner has rejected claims 22-34 under 35 USC § 112, second paragraph, for being indefinite and for failing to point out and distinctly claim the subject matter which Applicants regard as their invention. Claims 22-26, 30, and 31 have been withdrawn and claim 27 has been amended to clarify that the protein identified as PRO 243 does not comprise an extracellular domain, consistent with the art understanding of soluble proteins. Therefore this ground of rejection has been obviated and Applicants respectfully request rejection on this ground be withdrawn.

Rejection under 35 USC § 112, first paragraph:

The Examiner has rejected claims 22-27, 30, 31, 33, and 34 under 35 USC § 112, first paragraph, for allegedly not being described or enabled by the specification.

Applicants have withdrawn claims 22-26, 30, and 31, and therefore these grounds of rejection for these claims have been obviated.

Written Description

The Examiner has rejected claims 22-27, 30, 31, and 33-34 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants submit that claims 27-29, and 32-47 are adequately described in the specification.

Claim 27 has been amended to clarify that the protein identified as PRO 243 does not comprise an extracellular domain, consistent with the art understanding of soluble proteins. The claims are directed to SEQ ID NO: 7.

Applicants have withdrawn claims 22-26, 30, and 31, leaving only claims directed to the wild-type polypeptide. The specification recites distinguishing, identifying characteristics, sufficient to satisfy the written description requirement for the wild-type sequence, to which claims 27-29, 32-34, and 36-47 are directed. New claim 35 has a functional limitation directed to the ability of PRO243 to induce the switch from adult to fetal hemoglobin.

The specification therefore demonstrates that applicants are in possession of the claimed wild-type polypeptide because the sequence and consequently the structure of the claimed polypeptide are disclosed in SEQ ID NO. 7 (Fig. 4). In fact, several structural characteristics of PRO243, such as cysteine clusters, leucine zippers, and N-glycosylation sites are described at page 79 of the application.

Applicants also demonstrated possession of the claimed polypeptide by describing expression patterns and functional characteristics of the claimed polypeptide. For

example, at pages 97-98 of the specification, Applicants describe the expression of PRO243 mRNA in human tissues using a Northern blot analysis. At page 142 of the specification, Applicants describe PRO243's ability to induce the switch from adult hemoglobin to fetal hemoglobin in an erythroblastic cell line. Moreover, the Examiner acknowledges at page 5 of paper number 9, that the isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO. 7, with or without the signal sequence, meets the written description requirement of 35 U.S.C. § 112, first paragraph.

For all these reasons, Applicants submit that the specification recites sufficient distinguishing, identifying characteristics, sufficient to satisfy the written description requirement with respect to amended claims 27-29, 33, and 34. Applicants respectfully request the Examiner withdraw this ground of rejection.

Enablement

The Examiner has rejected claims 22-27, 30, 31, 33, and 34 under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled by the specification. Applicants respectfully submit that the pending claims are enabled by the specification and request reconsideration by the Examiner.

The Examiner noted that while the claims are enabled for the protein of SEQ ID NO: 7, with or without the signal sequences, or fragments thereof with either human chordin activity or fetal-hemoglobin inducing activity, the specification does not provide enablement for fragments or variants that are not required to have such activity, or for claims to the "extracellular domain" of the protein.

Applicants have withdrawn claims 22-26, 30, and 31. Applicants have amended claim 27 to clarify that the protein identified as PRO 243 does not comprise an extracellular domain, consistent with the art understanding of soluble proteins. Applicants have also amended the claims to clarify that fragments and variants are not within the scope of the invention.

Therefore pending claims 27-29, 32-34, and 36-47 are directed to the wild-type polypeptide disclosed in the specification in Figure 4 (SEQ ID NO:7) and are thus enabled

by the specification. Moreover, the deposit of PRO243 with the ATCC under accession number 209508 satisfies the enablement requirement. *In re Argoudelis*, 434 F.2d 1390. 1392 (CCPA 1970). Further the Examiner acknowledges that at least two uses of the claimed invention, dorso-ventral patterning and induction of fetal hemoglobin expression, are enabled by the present application. New claim 35 is directed to an isolated hemoglobin inducing protein comprising 90% sequence identity to the amino acid of SEQ ID NO:7.

Finally, the pending claims are directed to the wild type sequence of PRO243 or to a 90% variant thereof with a functional limitation and therefore reasonably correspond to the scope of enablement. Therefore, Applicants have demonstrated possession of the claimed genus as well as how to make and use the claimed genus and Applicants respectfully request this ground of rejection be withdrawn.

Rejection under 35 USC § 102:

Claims 22-26 and 33 are rejected under 35 USC § 102(e) as being anticipated by U.S. Patent Number 5,864,770 (LaVallie *et al*).

The Examiner notes that LaVallie *et al.* disclose human chordin at SEQ ID NO:2, which differs from SEQ ID NO: 7 of the present application at residue 70. Applicants note that while LaVallie discloses several assays utilizing the disclosed chordin polypeptide, each of LaVallie's examples are prophetic. In contrast, Applicants disclose several actual examples of assays utilizing PRO243. For example, at page 142, Example 36, of the present application, Applicants describe an assay demonstrating the ability of PRO243 to induce fetal hemoglobin in erythroblastic cells, at page 146, Example 37, Applicants discuss expression patterns of PRO243 seen in studies of human fetal face, head, and limbs and mouse embryos, and at page 148, Example 38, Applicants describe the activity of PRO243 mRNA in Xenopus Oocytes.

Applicants have withdrawn Claims 22-26 and therefore this ground of rejection for those claims has been obviated. Claim 33 is directed to a chimeric polypeptide comprising the polypeptide of Claim 27 fused to a heterologous polypeptide. Claim 27 encompasses the

wild-type sequence disclosed in SEQ ID NO: 7. This sequence is not identical to the sequence disclosed in LaVallie and therefore claim 33 is not anticipated. According to the MPEP § 2131, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of CA*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The *identical* invention must be shown in as complete detail as is contained in the ... claim." *Id.* Therefore, Applicants respectfully request this ground of rejection be withdrawn from claim 33.

Rejection under 35 USC § 103:

Claims 27-29 and 32 are rejected under 35 USC § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over LaVallie *et al.*, U.S. Patent No. 5,846,770.

Applicants submit that claims 27-29 and 32 are neither anticipated, nor obvious over LaVallie *et al.* because although, as the Examiner notes, sequencing errors can occur, one of ordinary skill in the art will recognize that a difference of even a single amino acid could have significant structural and functional effects. For example, mutations in residues that are required for structure formation or stability can have dramatic effects on activity. *See* Bowie *et al.* Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions. *Science* (1990) 247:1306-1310. Moreover, the single different amino acid of LaVallie's SEQ ID NO:2 is glutamic acid, which Applicants, at page 61, do not recognize as an amino acid that can be substituted for glutamine (residue 70 of Applicant's SEQ ID NO. 7) and still conserve the function and structure of the claimed polypeptide.

The Examiner also asserts that it is the Applicants' burden to provide evidence that the prior art disclosure does not actually possess the same characteristics as Applicants' SEQ ID NO:7. Applicants submit that the assay described on page 142 demonstrates that Applicants sequence, PRO243, has the characteristic of effectively inducing the switch from adult hemoglobin to fetal hemoglobin in an erythroblastic cell line. Nowhere does

LaVallie discuss the polypeptide encoded by SEQ ID NO:2 as having the characteristic of inducing the switch from adult hemoglobin to fetal hemoglobin.

Claim 34 is rejected under 35 U.S.C. § 103(a) as being unpatentable over LaVallie *et al.* in view of Hopp *et al.*, U.S. Patent No. 5,011,912. However, as discussed above, LaVallie does not render the polypeptide of claim 34 obvious because a difference of even a single amino acid can have significant structural and functional effects. Therefore, even in combination with Hopp *et al.*, LaVallie does not render claim 34 obvious. Applicants respectfully request that this ground of rejection be withdrawn.

CONCLUSION

Applicants respectfully submit that the application is now in condition for allowance. Should the Examiner feel a discussion would expedite the prosecution of this application, the Examiner is kindly invited to contact the undersigned.

Respectfully submitted,

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